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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/965,356	11/06/97	BERNFIELD	M	CMCC533

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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	13
DATE MAILED:	07/07/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/965,356	Bernfield et al.
Examiner	**Group Art Unit**
Anne-Marie Baker, Ph.D.	1632

☒ Responsive to communication(s) filed on *Apr 13, 1999*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed April 13, 1999 (Paper No. 10) has been entered. Claims 1-4, 7, and 10-13 have been amended. Claims 1-15 are pending in the instant application.

The following rejections constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Please note: The U.S. Patent to Saunders cited by the Examiner was made of record on Applicants' IDS.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transgenic mice expressing a syndecan from a transgene construct wherein the mouse is characterized by an obese phenotype and methods of using said mice, does not reasonably provide enablement for any transgenic animal expressing a syndecan from a transgene construct. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-6 are drawn to transgenic animals expressing a syndecan molecule, particularly syndecan-1. Claims 7-9 are drawn to a transgene construct encoding a syndecan. Claims 10-15 are drawn to methods for screening compounds which can alter body weight.

The specification fails to provide an enabling disclosure for the preparation and use of transgenic animals wherein a syndecan gene is integrated into the genome such that syndecan is expressed from a heterologous construct, because no guidance is provided in the specification for the preparation and use of such transgenic animals, other than mice. The claims encompass any animal having a syndecan transgene, but the specification is enabling only for mice. As discussed in the previous Office Action (pp. 4-6), phenotypic alterations resulting from the introduction of a transgene into an animal's genome cannot be predicted, even when the function of the gene is known. Thus the model system of Claims 10-15, wherein the transgenic animals are useful for the screening of compounds which can alter body weight is enabled only for transgenic mice expressing a syndecan transgene of the type disclosed in the specification. The phenotype of any other transgenic animal expressing an exogenous syndecan cannot be predicted and has not been demonstrated.

The specification fails to provide an enabling disclosure for the preparation of any species of transgenic animal of the type claimed because the phenotype of a transgenic animal cannot be predicted. In the absence of a transgene-dependent phenotype, one skilled in the art would not know how to use the claimed animals. The phenotype of any species of animal expressing a syndecan-encoding transgene as recited in the claim, cannot be predicted. The specification does not teach what phenotype would be expected in any species of transgenic animal of the type claimed, other than the mouse. Furthermore, the specification does not adequately teach how one would have prepared any and all transgenic animals expressing a syndecan-encoding transgene, because the specification does not teach constructs with appropriate regulatory regions

that would work in any animal, thereby imparting an obese phenotype to the resultant transgenic animal. The mere capability to perform gene transfer in any given species is not enabling for the claimed transgenic animals because a predictable phenotype cannot be achieved by simply introducing a transgene encoding a gene of interest. While gene transfer techniques are well-developed for a number of species, especially in the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse will not necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, there are inherent physiological differences between mice, birds, cows, fish, pigs, etc. that can affect the phenotype in an unpredictable manner. In the absence of representative working examples, the existence of any phenotypic alteration resulting from the introduction of a syndecan-encoding

transgene in any species of animal, is highly unpredictable. Without knowing the phenotype of the transgenic mouse, fish, cow, pig, or bird, one of skill in the art would not know how to use the animal. Given the lack of working examples, the limited guidance in the specification, and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic animals.

While the species-specific requirements for transgene design are not clearly understood, examples in the literature demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al., 1990 produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover any species of transgenic animal having a syndecan-encoding transgene, but the specification does not enable the full scope of the claimed animals. In the absence of disclosure of transgenic animals, exhibiting a transgene-dependent phenotype, representative of

the full scope of the claimed transgenic animals, undue experimentation would have been required to make and use the claimed animals.

The specification fails to provide an enabling disclosure for the preparation of any transgenic animals carrying a syndecan-encoding transgene construct other than mice. The specification describes the preparation of mice expressing a transgene construct comprising a nucleic acid molecule encoding syndecan-1 operably linked to the CMV promoter/enhancer regulatory regions, wherein expression of the transgene results in mice that exhibit maturity onset obesity. Syndecans have been identified in the mouse, rat, hamster, and human. However, other animals for which syndecans have not been identified, or for which the gene for a syndecan is not known, are not enabled for the generation of transgenics that overexpress a syndecan transgene. Furthermore, phenotypic alterations resulting from the introduction of transgenes is highly unpredictable. Given the lack of any demonstration of a maturity onset obesity resulting from expression of a syndecan transgene in any animal other than the mouse and given the unpredictability of obtaining a specific phenotypic alteration as the result of the introduction of a defined transgene construct, one skilled in the art would have been required to have exercised undue experimentation to have practiced the invention in any animal other than the mouse. Thus, limitation to mice carrying the claimed transgene construct is appropriate.

Applicants point out that the claims were rejected for animals other than mice on the basis that the animals must be produced using embryonic stem cell technology. This aspect of the rejection has been withdrawn. However, Applicants do not address the rejection with regard to the scope of the animals on the basis that the phenotype of any transgenic animal cannot be predicted. This rejection was made in the previous Office Action (Paper No. 8, mailed 10/9/98) on pp. 4-6 and 9. The complete grounds for the rejection is noted above and has been modified as necessitated by the amendments to the claims.

Applicants arguments concerning the rejection regarding the unknown melanocortin 4 receptor ligand have been considered (p. 5, paragraph 4 of the response). The rejection is rendered moot by the amendments to the claims and is therefore withdrawn.

Applicants arguments regarding the scope of the syndecan (p. 6, paragraph 3 of the response) is believed to be directed to the rejection on p. 9 of the previous Office Action (Paper No. 8, mailed 10/9/98). However, the rejection on p. 9 is directed to the scope of the animal not the scope of the syndecan.

Claims 4, 5, 7-9, and 13-15 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 4 and 5 are directed to a transgenic animal expressing a sydecan from a transgene construct, wherein the animal is characterized by an obese phenotype and further wherein the syndecan is expressed preferentially in the areas of the hypothalamus responsible for the regulation of body weight and energy balance. Claims 7-9 are drawn to a transgene construct encoding a syndecan, wherein the syndecan is preferentially expressed in the regions of the hypothalamus responsible for the regulation of body weight and enerby balance. Claims 13-15 are directed to methods of using said transgenic animals preferentially expressing the syndecan in the areas of the hypothalamus responsible for the regulation of body weight and energy balance.

The specification fails to provide an enabling disclosure for the transgenic animals wherein the transgene is preferentially expressed in the hypothalamus as recited in the claims, because there is no demonstration of preferential expression nor any mechanism known to drive this pattern of expression. Table 3 on p. 22 of the specification summarizes the tissue-specific expression of syndecan-1 in both wild-type and

transgenic mice. The syndecan-1 transgenic mice exhibited increased expression of syndecan-1 in heart, kidney, pancreas, skeletal muscle, and adrenal gland compared to wild-type mice. However, data for expression in the brain as a whole and localization of expression within the brain is not included in the table. Thus, a basis for comparison of expression in the brain with expression in other tissues is not provided. The specification (p. 23) discloses that expression of syndecan-1 was observed in the paraventricular, suprachiasmatic, lateral, dorso-medial, and arcuate nuclei of the hypothalamus, but does not indicate which other regions of the brain were tested for expression and what levels of expression were found. Since the level of expression in the brain is not given, no comparison can be made to the results of Table 3 which details the level of expression found in a variety of tissues. Therefore, it is not evident that preferential expression in the hypothalamus can be achieved in the claimed transgenic animals. Given the lack of working examples in the specification and the lack of guidance for employing a regulatory mechanism to drive expression of the transgene preferentially in the hypothalamus, one skilled in the art would have been required to have exercised undue experimentation to practice the claimed invention.

Applicant's declaration stating that Exhibit A (photographs showing syndecan-1 mRNA derived from the transgene expressed in the anterior and posterior hypothalamic nuclei) demonstrates unique expression of syndecan-1 in the transgenic mice to the hypothalamic nuclei regulating energy balance, namely the arcuate, lateral, dorsomedial, supraoptic, and suprachiasmatic does not address the fact that increased expression of syndecan-1 also occurs in other tissues of the transgenic mouse as discussed above. Thus, preferential expression in the noted areas of the hypothalamus is not demonstrated. The specification states on p. 23, lines 10-11 that the "elements in the transgene are sufficient to drive expression in the brain." However, the transgene also drives expression in other tissues, not only in the brain. No comparison is made

regarding the level of expression of syndecan-1 in other tissues and the relevant areas of the hypothalamus to demonstrate that expression within the hypothalamus is indeed preferential.

The specification fails to provide an enabling disclosure for the use of the transgene constructs of Claims 7-9, because it does not teach how to achieve hypothalamus specificity, as discussed above. As shown in Table 3, the CMV promoter/enhancer construct drives transgene expression in many tissues, including heart, kidney, pancreas, skeletal muscle, and adrenal gland. Chapman et al., 1991 report that the enhancer is active in a broad range of host cell types (p. 3979, paragraph 2). Given the lack of demonstration of hypothalamus-specific transgene expression and in the absence of any guidance regarding regulatory elements that can be used to drive hypothalamus-specific transgene expression, the artisan would have been required to have exercised undue experimentation to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 13-15 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 13-15 are indefinite in regard to the molecule that is "expressed preferentially in the hypothalamus" because it is unclear whether the preferential expression is with regard to other areas of the brain or the whole body. For example, the transgene may be expressed in a number of tissues throughout the

body and yet, within the brain, exhibit limited expression such that only particular regions of the brain express the transgene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7, 8, and 9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomsen et al., 1984 (W), Boshart et al., 1985 (X), and Saunders et al., 1996, U.S. Patent No. 5,486,599.

The claims are drawn to recombinant DNA constructs comprising a cytomegalovirus promoter including the intermediate/early enhancer and a nucleic acid molecule encoding syndecan-1, wherein the syndecan is preferentially expressed in the hypothalamus.

Thomsen et al. disclose the nucleotide sequence for the promoter of the major IE gene of human cytomegalovirus (p. 661, Figure 3). Thomsen et al. do not disclose the nucleotide sequence for the IE enhancer or syndecan-1.

Boshart et al. disclose the nucleotide sequence of the human cytomegalovirus (hCMV) enhancer region of the major IE gene (p. 523, Figure 3). The investigators also report that the hCMV enhancer shows little cell type or species preference. Boshart et al. do not disclose the nucleotide sequence for syndecan-1.

Saunders et al., in U.S. Pat. No. 5,486,599, disclose the nucleotide and amino acid sequence of murine syndecan-1 (SEQ ID NO: 1).

Since analysis of gene function and gene expression typically requires the use of recombinant constructs for controlled expression of known gene sequences, one would have been motivated to place the murine syndecan-1 gene under control of a ubiquitous promoter such that the gene would be expressed in cells transformed with the construct. One would have anticipated a reasonable expectation of success because only standard molecular biology techniques are required to make the construct and the structure and function of the CMV promoter are well-known. Furthermore, the CMV promoter has frequently been used to drive expression of exogenous genes because promoter/enhancer activity is known to be very strong relative to other known promoters (see Chapman et al., 1991, column 1, paragraph 2). Therefore, it would have been obvious to one of skill in the art at the time of the invention to have made a gene construct wherein the CMV promoter/enhancer was used to drive expression of syndecan-1 or any other known syndecan gene.

One would have been motivated to have combined the teachings of Thomsen et al., Boshart et al., and Saunders et al. in order to express syndecan-1 in a transformed cell line for analysis of the function of the exogenously expressed protein.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Applicants argue that the rejection under 35 U.S.C. 103 is improper because there is no motivation to combine the cited references and no expectation of success. Ample motivation is provided for making the constructs. As re-iterated above, the artisan would have been motivated to make the claimed constructs for *in vitro* studies to analyze the function of syndecan. Applicants do not offer any particular reasons as to why the stated motivation is "not sufficient." Thus Applicants' assertion is unsupported in this regard. Applicants further argue that the art cited does not indicate that the combination of a CMV promoter and syndecan gene would result in preferential expression in the hypothalamus. The art does not need to indicate

this for the following reasons. First, the claims are directed to compositions, not methods of using those compositions. Thus the claim language "wherein the syndecan is preferentially expressed in the regions of the hypothalamus responsible for the regulation of body weight and energy balance" is not given any patentable weight. The function of the constructs is an inherent property of the constructs. Second, the motivation for combining the references is not to achieve hypothalamus-specific expression of a transgene in a transgenic animal, but to study syndecan function *in vitro*. This is ample motivation for making the claimed constructs.

Applicant is advised that the disclosed transgenic mouse with a syndecan-1 gene operably linked to regulatory regions that drive expression of the transgene such that the mouse exhibits maturity onset obesity is enabled by the specification but not expressly claimed as such. The assay for screening compounds which can alter body weight is also enabled for the same scope as the animals. Claims limited to transgenic mice carrying a transgene construct of the type disclosed, wherein the mice exhibit the disclosed phenotype are appropriate.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.
July 5, 1999

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630